# HARVARD MEDICAL ALUMNI BULLETIN

April, 1954

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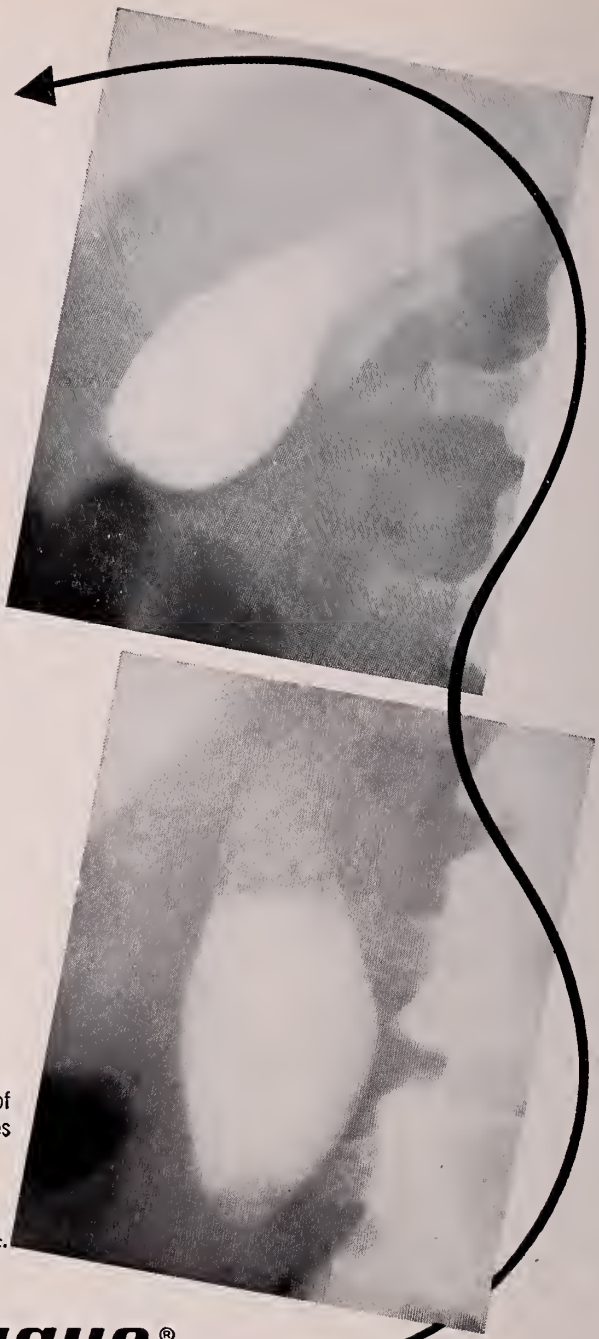

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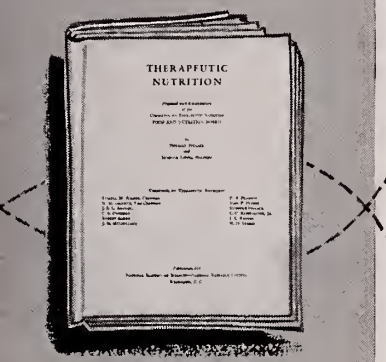


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* Therapeutic Nutrition, Committee on Therapeutic Nutrition, Food and Nutrition Board, Publication 234, National Research Council.

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# Harvard Medical Alumni Bulletin

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## Contents

# *General Practice in a Small Vermont Town*

RALPH R. JARDINE, '35


THE AUTHOR ON THE STEPS OF HIS OFFICE

Fourteen years ago, after two years of a rotating internship and two years' residency in chest diseases, the opportunity to go into general practice in Lyndonville, Vermont presented itself to me. The decision was fraught with difficulty. I was a stranger to Vermont, I had more or less grown up medically in the aura of the great teaching hospitals, and I wasn't sure exactly what I did want to do. However, I felt that general practice might be the best way to develop self-reliance and increasing skill in the art of correct diagnosis arrived at by the use of a good history and physical examination—an art even then being lost sight of in the maze of laboratory data beclouding simple physical diagnosis. Consequently, I decided to try general practice in a small town for two years, as a sort of proving ground. How well it has worked out may be assumed from the fact that I am still here after fourteen years, and have no intention of leaving—ever!

Lyndonville is a remarkably pleasant little northeastern Vermont town of 2000, 185 miles from Boston and 30 miles from the Canadian border. It has a good business center, up-to-date schools, a State Teachers College, and many opportunities for outdoor activities. Formerly a railroad center, its economy now is based on a few small industries and on its role as a trading center for eight surrounding smaller towns. More and more small farms are being bought by city dwellers (often college teachers) as summer homes or as havens for eventual retirement, and in winter the population is swelled by large numbers of winter sports enthusiasts, for we have skiing facilities the equal of any in the East. The country is hilly and wooded, with numerous trout streams for the fisherman, and the roads, for the most part, are good. The winters are cold, the thermometer often dipping down to forty below, but the air is dry and clear. I have often been much colder in Boston, with the temperature above zero and the wind whistling in off the ocean.

The six or eight surrounding towns have no doctors, and so in a way Lyndonville is the medical center of the region, with a population of about 8000 to care for within a radius of 20 miles to the north, east and west. This involves a good deal of driving (about 2000 miles a month) but fortunately people are now increasingly willing to come to the office if at all able to travel. There are two hospitals available in St. Johnsbury, nine miles to the south, plus the services of

several specialists in various fields; and 75 miles away in different directions are the medical centers of the Mary Hitchcock Hospital in Hanover and the University of Vermont Medical College in Burlington.

My first year was rather rugged, what with learning to drive on icy or mud-rutted roads to unknown farms on unknown back roads in the middle of the night, but soon I began to get fairly familiar with local geography. Next came increasing knowledge of the family histories of my patients—what they had done in the past, what they were doing now, what kind of lives they had led—all bits of information that led to more adequate treatment of their psychic and/or somatic ailments. Suspicion of the "new doctor" and the natural reserve of the Vermonter (he doesn't extend his friendship or his acceptance until he is sure of his man—but then he is a friend for life) had to be overcome, and the quirks of the local mores understood and complied with. But after a period of adjustment and shaking down, I began to find myself at home, and ever since I have increasingly enjoyed the life of a country and small town general practitioner.

The actual practice of general medicine in the country differs little from that in the city, I suspect. However, the small town doctor lives more closely with his patients and from daily observation soon comes to know what makes them tick. A great deal of his work may be routine (and the temptation to resort to symptomatic treatment is ever-present) but he must be alert to recognize the unusual or the serious, too. A good history and a good physical examination, plus a few simple office laboratory procedures, will make the correct diagnosis the vast majority of the time, and here in Vermont, the services of a specialist and complete laboratory facilities are available within traveling distance of any patient who needs them. So I feel that the medical means available within the small state of Vermont are as good as in our metropolitan centers. What the doctor does with what is available depends upon him—he can become a rural pill peddler or he can adequately treat the majority of his patients himself, and quickly direct those needing specialized care to its readily available sources. Whether the patient seeks that care depends on the tact and wisdom of the doctor, and the general practitioner who has lived and worked and occasionally played with his patients can well direct them.

I think one of the most satisfying things about practice in a small country town is the intimate sense of being part of the community that one develops. The doctor is looked up to far more than his city colleague, it seems, and his advice is sought on many non-medical matters. As a corollary, he in turn develops a fierce loyalty to the town and can do a great deal towards its betterment. Of course, being more or less in the public eye, the doctor has to watch his own standards of public behaviour, perhaps a bit more than his city colleague, or there will inevitably be some gossip. Gossip can be the bane of the small town, but in Vermont it is not too much of a problem, for the right of the individual to be a nonconformist is recognized and appreciated. Gossip, in a way, keeps the doctor on his toes, for it is surprising how fast news of a fancied medical mistake gets around town!

The financial rewards of a small town practice in Vermont are not outstanding, but the doctor usually makes as much as anyone in his town, and has a comfortable living. His overhead isn't as high as it would be in the city, and his net income is greater proportionately. However, living costs are about the same, and gas and fuel, and even food, are apt to be higher. The proportion of his fees he collects depends upon how realistic he is in setting them in respect to his patients' incomes, and he knows the majority of his patients will pay him if they can. He does no free work in the hospitals as in the city, but nevertheless, sees a great many patients he knows cannot pay him. He may be rewarded by the gift of a box of homemade candy from some poor family at Christmas, and he knows that his services are

appreciated. In Vermont, the proponents of socialized medicine are few and far between, and I think it is because, by and large, the doctors of Vermont have succeeded in providing the people with good medical care at prices they can afford. Blue Cross-Blue Shield coverage is widespread and the principle of voluntary health insurance is well understood and appreciated. However, no compulsory health insurance originating in Washington is apt to interest the average Vermonter.

About a year ago, another doctor and I decided to join forces, and, after converting a large old house into shared offices, formed a small group practice. Our main object was to try to overcome the most undesirable aspects of country practice—the medical isolation and lack of free time either for study or relaxation—and it has worked out well. It enables us to utilize more adequate x-ray and laboratory equipment than one man could afford, it makes informal consultation on puzzling cases readily available, and since one man takes alternate evening office hours and night calls, and is willing to cover when the other wants to go away, it affords the necessary time for relaxation and study. It is good for the community, for emergency medical service is always available, and it is appreciated by the people. It is important to preserve the individual patient-doctor relationship, however, and each man takes care of his own patients individually.

General practice in a small country town is a satisfying experience, provided a man is interested in people, and one can find as rich and varied a life as in any type of practice anywhere. But the dangers of medical isolation—brought on mainly by fatigue and the lack of time for study—are real, and I think can best be solved by the group practice of medicine as I have outlined it. Not every small town in Vermont would be a good place to live, but in almost every section of the state there is an attractive town, not far from good hospital facilities, where two doctors could practice and cover the surrounding area. The opportunity exists, and to my mind it makes the general practice of medicine in the country a career that many more Harvard men should consider.


The Covered Bridge is not yet Extinct in Vermont

# *Comments on Medical Research with Particular Reference to Short Term Project Grants*

DOUGLAS A. FARMER, M.D. '42
Instructor in Surgery,
Boston University School of Medicine

A growing national awareness of the vital importance of medical research has in a relatively few years resulted in the availability of tremendous funds for investigative activity by medical schools, hospitals and laboratories. In earlier years such research was financed largely by income from endowment, special gifts from foundations, research institutes and private individuals, occasionally by unrestricted medical school funds and in several instances by the investigators themselves. Government participation in medical research was restricted primarily to investigation carried on by the medical services of the armed forces and the United States Public Health Service. For obvious reasons the advent of World War II prompted the government to take a large and direct interest in medical research with particular reference to grants-in-aid to institutions already equipped to carry out research projects. In a time of emergency the selection of such institutions was dictated by a necessity to achieve results in the shortest possible time.

The attitude of the government did not change with the cessation of hostilities. On the contrary, appropriations have increased year by year. It was feared by many that as the government took a progressively larger part in the financing of medical research that funds thus appropriated would gradually supplant the private sources of income for this purpose. The reverse has proven true. Such privately administered endeavors as the American Heart Association, the National Foundation for Infantile Paralysis, and the National Cancer Society, supported primarily by public contribution, have kept pace with the federal government in provision of funds. Other older institutions such as the Rockefeller Foundation continue their support as before. The sum total of all this has been to provide great impetus for increasingly productive investigation in almost every field imaginable. It likewise produces a progressively more complex administrative burden and, as has been frequently stressed in the past few years, has placed a great financial load on the recipient institutions. It seems paradoxical that many medical schools have had to place restrictions on the acceptance of grants by members of their staffs because the schools themselves could not afford it.

A considerable amount of the available money is applied for and received by part- or full-time clinical members of medical school or teaching hospital staffs. It is with particular reference to this category rather than to the full time preclinical scientists that the following comments are made. The activities of these clinical investigators include teaching medical students, taking an active part in the care of the ward patients in their institution, carrying out their research program and, in many instances, conducting a private practice,—the latter a basic necessity as most of these men have families to house and feed.

It may be worth while in this Bulletin to discuss several of the factors relating to project financing by short-term grants inasmuch as a surprising percentage of the Alumni of Harvard Medical School are engaged in part or full time academic activities.

Should a man have a problem he wishes to investigate, several sources of funds are open to him. A few of the prominent private institutions have been named. Many others are listed. Among government agencies the Public Health Service, the Atomic Energy Commission, the Office of Naval Research and the Veterans' Administration allocate funds for large numbers of grants. The Public Health Service is probably the largest single donor agency. A committee appointed by the Surgeon General of the Public Health Service to study medical school grants and finances pointed out that in the year 1947-1948 approximately one-half of medical school research budget ($17,100,000) came from federal grants and contracts, while industry, private associations and foundations accounted for most of the remainder. The Public Health Service alone accounted for one-half of the federal support or about one-fourth of the total budget. Although the pattern of planning and application through most agencies is in general similar, any reference to detail in subsequent remarks is based on the writer's experience with the Public Health Service.

In most instances the application form is detailed and specific and the agency demands a concise outline of the over-all aim of the project and an accurate description not only of the proposed plan of attack but also the facilities available (including personnel) with which to carry out such a plan. Also requested is a summary of the work done by the applicant and by others in the field covered by the application and a statement of the potential benefit such an investigation might bring to medical science in general. A budget, specific to the last detail, must be presented. Herein lies one of the greatest pitfalls, since the estimation of precise need and the division of requested funds for an initial grant requires experience.

Planning in advance on non-professional personnel is a difficult aspect of the problem, particularly in the case of "short-term" grants. Such grants are generally allotted for one year, perhaps with provisions made for one or two years' additional support on modified reapplication. Several months to a year will usually elapse between time of application and activation. One must provide himself with technical and secretarial help on fairly short notice and can assure only one or at the most two years' employment. Because of this the caliber and dependability of non-professional help may suffer. On such terms only young and inexperienced personnel may be available. All too often one is forced to employ a young married woman who is simply putting in time until her husband finishes school or hospital training. It is difficult to hold such a person to strict terms of contract and of course, the hazard of pregnancy is real. Few investigators get through many years of short term grants without having their carefully laid plans marred by the sudden resignation of a trained technician followed by a week of frenzied search for a replacement and a month of training the recruit. It has been wisely said that the only dependable technician is a pensioned spinster in whom the bloom has begun to wither and upon whom a hysterectomy has been performed.

Continuity of support is a major consideration in planning one's project. Some investigations can be completed in a year or less but many will require several years before sound conclusions can be reached. Clinical investigation which often requires prolonged patient follow-up study falls in the latter category. Thus if one embarks on a clinical investigation which may require an indefinite period to reach sound conclusion he must have in mind that his grant may be terminated in the midst of his study. In such a case if the institution with which he is associated is not prepared to stand the expense of completion of his study his time may well have been wasted.

Occasionally as one proceeds with a course of study, certain promising side lines open up which might be profitably pursued. Sometimes such ramifications have a more major implication than the original study. Leeway in the decision to

follow such promising leads is important not only from the standpoint of individual interest but also from the point of view of increased productivity of medical research at large.

Most donor agencies are fully cognizant of the importance of continuity of support and the desirability of individual freedom in the decision to investigate certain leads not described in the grantee's application.

The government donor agencies and particularly the Public Health Service are notably fair in this respect. They make no bones about the fact that their basic philosophy includes painstaking scrutiny of the proposed project and more important, the principal investigator himself. Once having made a decision they will back an investigator generously and not only permit but encourage him to pursue a promising side issue if in his opinion it may turn out to be of real value. Such freedom of inquiry is part of the philosophy "support the man rather than his project." It is unthinkable that any donor agency should wish to exercise control over research in progress unless such an agency has arranged by contract for a certain group to work out a specific problem. In the case of the Public Health Service, freedom of inquiry is guarded by about 200 staff members of medical schools and universities who comprise the personnel of the study sections and advisory councils. It is their duty to survey and act upon grant applications.

Utopia in the realm of continuity of support and freedom of activity is embodied in the Career Investigatorships awarded by the American Heart Association, outlined elsewhere in this issue. In this instance a man is given a lifetime career of research, an adequate salary, a pension and money for technical help and supplies. He may select whatever project he wishes and has freedom of choice of place of work. Such a fellowship will usually be awarded to a basic scientist since it represents a career for which he has been trained. Few men carrying out clinical investigation of the nature referred to in this discussion would be fitted for or willing to accept a position which would lead them completely away from clinical medicine. For most of the clinical group research and teaching afford real stimulation but their basic interest lies in the diagnosis and treatment of disease.

A discussion related to the problems of grant supported research must include a consideration of the impact of such programs upon medical schools and teaching hospitals. It was mentioned earlier that many institutions have been obliged to restrict acceptance of such gifts because they could not afford to spend them. The cost of conducting research programs has been the subject of careful analysis in recent years. Total cost of a research project may be divided into direct cost and indirect cost. Direct cost or the amount of the grant-in-aid refers to the money utilized for equipment, expendable and non-expendable supplies, salaries for technical and secretarial help and in some instances a portion of the principal investigator's salary. Indirect cost refers to money spent by the grantee institution in order to carry out the research program but not included in the grant-in-aid. Laboratory space, the rental of which is rarely included in the grant, heating, lighting, maintenance, use of the library and certain administrative functions are included in this fraction. Perhaps less tangible is that portion of the investigator's income paid by the medical school for teaching purposes, when all too frequently time intended for teaching is sacrificed on the altar of research. In many instances grantee institutions have been forced to meet the added costs of extensive research programs by using funds intended primarily for educational purposes. In the case of the teaching hospital such costs simply serve to increase the yearly deficit.

Such indirect cost might be logically covered by the donor agency as overhead. It is a somewhat philosophic matter as to just where the duty of donor agency lies in this matter. Certainly some attempt should be made to help the grantee insti-

tution defray the indirect costs. On the other hand it seems only logical that an institution should have some stake in the work going on within its walls. If a medical school is unwilling to back to some extent work carried out by one of its own staff members, donor agencies might reasonably be expected to adopt the attitude that such applicants probably represent bad risks.

The truth of the matter is that most medical schools pay heavily in support of their research programs and that many donor agencies contribute to indirect cost by alloting a certain per cent overhead with each grant. The discrepancy appears to lie in the difference between indirect cost and the amount granted for overhead. Various agencies use different formulas in the computation of overhead ratio. In most instances after individual projects have been approved a certain per cent of the total is added to cover indirect cost. Thus the Public Health Service allows an 8 per cent overhead and gives the grantee institution permission to keep permanent equipment. As it has been estimated that approximately 7 per cent of all grant funds goes toward purchase of permanent equipment, the total amounts to about 15 per cent. The National Science Foundation proposes to allow 15 per cent of the total cost as overhead and to permit the institution to keep permanent equipment. Some federal agencies retain title to such equipment. Frequently in the case of gifts on the part of individuals no provision is made for overhead. It is to be noted that in the case of the Career Investigatorships awarded by the American Heart Association an overhead of approximately 5 per cent is allowed.

Studies at various institutions by outside agencies have shown that it costs medical schools approximately 35 per cent of the total amount of direct expense to provide adequately for indirect expense. In a recent thorough analysis of this problem appearing in the Journal of Medical Education, Dr. H. M. Weaver, director of research for the National Foundation for Infantile Paralysis, concluded that in order to defray 90 per cent of indirect costs a donor agency would have to allow 46 per cent overhead for grants of $10,000 or less and somewhat lesser amounts for larger grants.

The overhead problem has been discussed in some detail, because any influence which bears heavily upon the cost of medical education is of interest not only to medical schools and physicians at large but to the nation as a whole. Cost of medical education increases year by year. Although tuition, gifts, endowment and appropriations also increase they are not keeping pace with the rising costs. Most medical schools expend several times the amount received from a student to graduate that student. It is a sobering thought that one of the nation's outstanding universities is seriously considering relinquishing the teaching of medicine because of the fact that approximately 60 per cent of its over-all income is spent in producing 5 per cent of its yearly graduates.

Those who view with horror the possibility that the federal government may have to share the increasing financial burden of medical education might take heart from the fact that the expense of medical research is shared about evenly by the government and by publicly supported private donor agencies. As far as the research worker is concerned, the quality and quantity of support are much the same and the lack of interference on the part of the donor agencies is almost identical. We may take some heart from the fact that if government funds for medical education can be administered as generously and intelligently and without trace of political manipulation as are the enormous funds appropriated by the government for medical research, there is little cause for worry that political vagaries might prove detrimental to the production of soundly trained physicians.

# *Doctors Coons and Pappenheimer Awarded Career Investigatorships*

Two members of the Medical School Faculty, Doctors Albert H. Coons and John R. Pappenheimer, have been named Career Investigators by the American Heart Association.

The two new investigatorships, which are unique in the field of research, bring to three the number of scientists receiving support from the A. H. A. throughout their productive lives. Dr. Victor Lorber, the first Career Investigator, appointed in 1951, is now conducting studies at the University of Minnesota of chemical processes within the heart muscle.

Dr. Pappenheimer, '37, newly named Visiting Professor of Physiology at the Medical School, has centered his recent studies on the way the blood nourishes body tissues. During World War II, Dr. Pappenheimer worked on the development of oxygen equipment for high altitude flying in military aviation. A native of New York, he joined the Faculty of Harvard Medical School in 1946, becoming Assistant Professor of Physiology in 1949. Previously, he was an instructor at University College, London, and at Columbia University's College of Physicians and Surgeons.

Dr. Coons, '41, newly named Visiting Professor of Bacteriology and Immunology, has been working in the field of immunity and has developed a new tracer technique using the dye fluorescein, to study the distribution, interaction and characteristics of antigens and antibodies in the animal body. A native of Gloversville, N. Y., Dr. Coons began his investigations at Harvard in 1940 as a National Research Council Fellow. He served with the U. S. Army Medical Corps in Australia and New Guinea during World War II. Returning to Harvard in 1946, he became the Silas Arnold Houghton Assistant Prof. of Bacteriology and Immunology.

Under the Investigatorship program, the investigator is enabled to work independently on research of his own choosing relating to cardiovascular problems. He spends his entire time in research and teaching, with not more than 15 per cent of his time to be spent in formal scheduled teaching (including Ward Rounds). The minimum stipend is $12,000 annually. It is the intention of the A. H. A. to support the investigator in research until he is 65 years of age and he will come under the retirement plan of the Association.

The investigator may work in any institution in the United States which offers adequate research facilities and he may move from one institution to another, including brief periods outside the United States. A maximum of $7,500 annually is made available to each investigator for technical help, secretarial services and supplies. The institution where he works receives $1,000 for overhead.

# *Editorial*

## The Problem of Short-term Grants for Research

The announcement of the award of two Career Investigatorships of the American Heart Association to members of the Faculty of Medicine has a far greater significance than the obvious boon it is to the Harvard Medical School and to preclinical research. As has been pointed out elsewhere in the present issue of this Bulletin, the problem of financing medical research bears directly on the cost of medical education and is thus of concern to those who may not themselves be involved with research as such. That the financial support stems from sources outside the University does not ease the strain on the Medical School or on the budgets of the affiliated Hospitals. Paradoxically, the circumstances under which most short-term grants for research are made may actually add to the financial burden. The magnitude of this burden may be estimated from the following figures: For the fiscal year, 1952-53, research monies available to the Harvard Medical School from outside sources approximated $2,000,000. Considering only the monetary aspect, and employing the data quoted by Dr. Farmer in the present issue, one can predict a net cost to the Medical School for indirect expenses from this transaction of about $500,000. This is startling. Even more startling is the fact that these figures do not include 130 fellowships supported by outside funds (varying from $3500 to $6000 per annum) awarded to the Medical School for the same year. In this case the costs to the institutions involved are less tangible, but they are none the less real.

A part of the cost of present research programs, and no small part, is the necessity for yearly processing and administering short-term grants. The Career Investigatorships do away with the necessity for repeated applications for new funds for research projects and personnel. From this point of view alone, they represent a considerable saving in effort as well as in dollars.

In sponsoring a man rather than a project, the American Heart Association has brought to fruition an aim that the short-term grants have only partially achieved. Financing the individual is of necessity a long-term commitment. For the University such a long-term commitment means, according to Dean Berry, "that the Faculty has been enriched by the addition of two distinguished professors, whose financial support stems from what would be the equivalent of at least $1,000,000 of endowment." For the individual investigator, it means—in the words of Dr. Coons—"the removal of some of the fetters on the imagination that anxiety about the future always imposes."

A more subtle, but equally important, aspect of the problem is suggested by the current contribution to the Bulletin from two members of the fourth-year class. In a discussion of certain aspects of medical edu-

cation, they mention that "the complexity of the problem is compounded by the fact that the doctors involved (in teaching) must assume the combined role of investigator-teacher-clinician. This academician is sorely tried to produce satisfactorily in any one of these positions." The tension developed by this three-way stretch is further aggravated for the investigator dependent on short-term grants by the applications, progress reports, uncertainty of technical help, and even of financial support for himself. The demand on the investigator is highlighted by a paragraph from Dr. Pappenheimer's comments on his award. "Indeed, we lacked only one important thing, and that was *time,* time to test ideas, time to plan and study experiments and time to browse in quest of new ideas. For me the Heart Association Award is primarily a grant of TIME—that most precious of all laboratory equipment."

The crushing load of teaching and administrative responsibility, which often keeps an investigator out of his laboratory, is an unfortunate necessity in an institution one of whose prime purposes is teaching medical students. Its financial support therefore implies an obligation primarily to this purpose. For the clinical investigator, whose task is complicated by patient care, the burden may be a lethal one, frequently for his research program and occasionally for him himself.

For these reasons the "fifteen per cent of time" limitation on formal teaching imposed by the terms of the Investigatorship is intended to free the teacher for unhampered research. Yet implicit in these terms is the fact that some time should be spent in teaching—a necessity for the full development of the investigator and of his program. This fact is fully realized by both of the newly appointed Career Investigators.

"There are two reasons for a continuing relation with teaching and the business of the University, both compelling," says Dr. Coons. "The first is the stimulus which contact with students provides and which is a lifeline out of the ever-narrowing vortex of a special interest. The second is to mitigate the delicate position of the chronic guest, who always runs the risk of becoming a trial."

In commenting on his award, Dr. Pappenheimer says further, "I do not mean to imply that we shall now retire into an insulated world of research. I hope to be allowed to continue to teach and to take part in the departmental and inter-departmental activities of the Medical School and the Division of Medical Sciences. I hope that our work will be sufficiently exciting to attract graduate students and visiting fellows as it has in the past. Finally, I hope that my contribution to the teaching activities of the School (though necessarily more limited than in the past) will lighten substantially the teaching load of my successor in the Department of Physiology."

The American Heart Association has taken a significant step toward helping in the solution of the complicated problems besetting a career in academic medicine.

J. P. M.

*Inside*

*H. M. S.*

# *"Thirty Years of Transition"*

ROBERT H. JONES and SCOTT ADLER, '54

What was wrong with medical education thirty years ago?

To all generations of H. M. S. students, Alumni, and Faculty, there has been a desire that medical education be modified and improved in terms of the current problems and technics. In a measure this depends upon how successfully the problems are defined and eventually solved within one generation, rather than modifications of a more distant nature. In this respect the student of 1954 can further delineate the current needs and the Alumni of 1920 can re-evaluate their achievements by reviewing and comparing the last thirty years of medical education at Harvard.

In 1922 Dr. Elliot C. Cutler, later Chief of Surgery at the Peter Bent Brigham Hospital, spoke before the Medical Exchange Club and expressed dissatisfaction with the existing trends in medical education. It was his opinion that teaching had become too didactic, that too much time was being devoted to the minor specialties, that there was a lack of correlation between the clinical departments, and that the subject matter was allowed to overlap excessively. He felt that there was too little "freedom for the students . . . . to digest the mass of facts which each day (was) hurled at them."

To the student of 1954 these criticisms sound strangely familiar. At any student bull-session today one or all of the above complaints are commonly mentioned. Yet, somehow, the contemporary student feels he is uniquely subjected to an overwhelming work load. This has developed from his realization that the last quarter of a century has produced an immense fund of knowledge that did not exist to plague the former student. It would not seem possible then that the above criticisms could have any validity in 1922.

But is such the case? It would appear

that it was not, for in 1922 the student had a volume work load even greater than that of today. Then, the catalogue hour requirement for graduation was 4965 hours. In 1953 it was 4374 hours. This 600-odd hour difference, or the equivalent of a half year of work, was in large measure an addition to the pre-clinical years. In 1920, morphology both by didactic lecture and laboratory study demanded more of the student's time than today. Didactics prevailed even through the fourth year where the student spent one day a week in the lecture amphitheater. His fourth year clinical experience was even further limited in that a majority of his time was spent on either medicine or surgery.

It can be seen that in the mastery of this volume of work, the student was obligated to work equally as hard and diligently at his studies as is the student of today. Therefore, the student of the 1920's could righteously offer such criticism of his education.

Since then the trend has been to enact modification of the type that Dr. Cutler's criticisms outlined. Yet this alone has not been sufficient to cope with the continued need for further modifications. This can be seen in that the criticisms still remain despite the changes.

As part of the continued attempts to further perfect the over-all teaching, student curriculum committees are currently studying the program of medical education at Harvard. Working with the Faculty, they are seeking changes in emphasis, suggesting topic deletions or additions, and noting what they consider to be points of weakness or duplication in the curriculum. They ask for more didactics or less as is currently appropriate. In other words it might be said that they are endeavoring to see that Dr. Cutler's suggestions are carried out.

Still, the conditions are such that medical knowledge continues to accumulate faster than it can be effectively categorized, presented, and assimilated. Thus it may be questioned whether shifts in the curriculum alone can produce an environment wherein assimilation of knowledge can keep pace with the advances in the body of scientific knowledge.

If establishing an accurate and complete curriculum is not sufficient, then it would appear that other aspects of medical education require further consideration. Once again in 1922, Dr. Cutler accurately forsaw this when he said perhaps the curriculum is after all not as important, but "it is rather the ability of the teacher to teach that is so essential."

Successful teaching demands that the teacher provide a carefully planned and integrated introduction to the factual body of medical knowledge. To provide this introduction, the teacher has to be sufficiently capable in the areas of investigation and research in his field to accurately evaluate recent developments. Moreover, to present all this to the student, he must intelligently assemble the masses of data and from them prepare his contribution to the didactic program. This demands careful and rigorous preparation by combination, deletion, and simplification to be maximally effective in the terms of teaching value. To do this well is the mark of the good educator. He is one who knows not only his subject but also effectively understands the variables affecting the learning situation.

Results are measured in terms of a successfully acquired and thoroughly understood foundation rather than striving for quantitative presentation of complex, but often ill understood, facts. A basic introduction to medical knowledge that is thoroughly understood is a better stimulus to further self-education than is mere exposure to obscure but brilliant researches.

Here then is another important concept if further attempts to improve the methodology of medical education are to be successful. Greater stress may well need to be placed upon encouraging the medical teacher to understand the dynamics of the educational process itself. This in turn will provide the medical schools with educators as well as investigators. Such an excellent

educator-investigator produces and assembles his facts so that a concise, logical, and comprehensive work is presented, at the proper time, for the consumption of the medical world. In a like manner his lectures are equally as carefully prepared. To state that this as a goal is not sought nor that contemporary Faculty are not concerned with their ability to teach would be naive and untrue. Yet this appears to be only an individual concern and not a matter of school policy.

The essential combination between a balanced curriculum and capable educator would help to lead to a more efficient and successful program of medical education. It would seem, then, that the problems in present day medical education transcend any one small aspect of medical school teaching and learning. They are derived from and in turn affect all the aspects of the medical profession. The complexity of the problem is compounded by the fact that the doctors involved often assume the combined role of investigator-teacher-clinician. This academician is sorely tried to produce satisfactorily in any one of these positions.

The relevance of this problem to the medical student is immediately obvious if one realizes that about 60 per cent of today's fourth-year class will eventually become engaged in some phase of academic medicine in the future. Therefore, the obligation for discovering solutions for these problems rests as squarely on the current fourth-year class as it does on any of the medical elders.

# *Doctor in the Sandwich Islands*

WILLIAM TOTHEROW, '51

Lanai is the smallest of the inhabited islands in the Hawaiian chain with the exception of Niihau which is populated entirely by Hawaiians. These Sandwich Islands were termed by Mark Twain, "The most beautiful fleet of Islands anchored in any ocean," and the spirit of the people, the way of life, the unending beaches, deep jungles, all keep calling one back once he has left Hawaii.

This was my situation on being released from the USAF a year ago—Hawaii was calling. I had been here off and on since December 1941, served my internship at Tripler in Honolulu, and developed a feeling for all that is Hawaii that couldn't be denied. As a result, I accepted the position on Lanai as assistant plantation physician, having contacted the proper persons through my old friend, Dr. Nils Larsen, the Kahuna-Lapa-au, or medicine man of Hawaii.

Lanai, a geographically insignificant spot on the vast Pacific Ocean, is nevertheless the largest pineapple plantation in the world. There are 26,000 acres under cultivation and the constantly ideal climate permits year-'round planting and harvesting. From the air the terrain presents a beautiful mosaic of green fields with borders of red volcanic earth which can be dry powder one instant and a hopeless mass of clinging mud the next instant in a tropical downpour.

From Kaumalapau Harbor on the south side, the island rises in terraces to a height of some 3,000 feet. There are two distinct, but long since extinct volcanoes, which are now worn down to a shallow saucer shape and are excellent for pineapple cultivation. Volcanic action on the island of Hawaii, however, is constant and frequent tremors are felt here on Lanai. The last activity resulted in a rain of lava nine miles long and a mile wide along Maunaloa in 1950.

Hawaiian Skies and Palms

Hawaiian culture flourished on this island over 500 years ago as evidenced by carbon age determinations in strata of cooking fires at old camp sites. Recently I was privileged to accompany an archaeological expedition to an old Hawaiian cave

which produced many valuable discoveries in the study of ancient Hawaiian lore. Prior to the influence of European culture there was no written language and as a result most of the facts concerning old Hawaii are obscure. Much has been handed down by word of mouth and constitutes the vast majority of our knowledge concerning this unique race. Exactly where the first Hawaiians came from is a mystery, but their physical and social characteristics definitely establish them as true Polynesians as distinguished from Melanesians and Micronesians. Their close cousins inhabit Samoa. Books have been written on the subject and present a fascinating story of a hardy, resourceful, and community-conscious race. Since the middle 1800's all races of seafaring men have been attracted to the Sandwich Islands and their beauty. As a result, the admixture of races now is unending and the pure Hawaiian exists only on the island of Niihau and in very isolated areas of the other islands. Caucasian and Oriental influence is apparent everywhere. Philippine, Portugese, German, Dutch, English and all the other recognized racial and social groups have so mixed that here we have a true "United Nations" living in harmony and peace indulging in a way of life that has no peer.

Hula Troupe Combining Five Nationalities

Medicine in the Islands has been a recognized profession since the beginning of Hawaiian culture. The Kahuna-lapa-au was in possession of numerous herbs used in the healing arts, some of which are still recognized as valuable therapeutic agents. Dr. Larsen has made an extensive study of this art and some of my most enjoyable and profitable hours have been spent in listening to his dissertations.

But, back to Lanai. According to legend, the first inhabitants were the Menehune or fairies, and subsequently a fishing village sprang up on the south side of the island some 500 years ago. Later, large colonies developed on the Keamoku side facing the island of Molokai across a nine-mile strait. Around the turn of the century a ranch flourished here and the old keawe fences are still to be seen, as are occasional old cowboys who still remember the early days. Hawaiian (Dole) Pineapple took over the island some 30 years ago and gradually increased pineapple production till now Lanai is known as the Pine Isle.

Our population is around 2,500-2,800 people and varies somewhat with working conditions and available employment. Again, almost every race is represented, but Filipino field workers predominate. Most of the supervisory and managerial positions are held by Caucasians or Haoles (pronounced "Howlie") most of whom are Malihinis (newcomers), but some are Kamainas (oldtimers) born of missionary parents or seafaring people who came early to the Islands. There are many orientals, Japanese and occasional Chinese, most of whom have intermarried now. The total population is swelled by some several hundred deer, dogs, and fighting chickens. Cock-fighting is a favorite pastime of a large per cent of the population rivaling bull fighting in Mexico or football in the U. S. The custom is frowned on by local gendarmes, but this seems only to enhance the pleasure of the sport and increases the financial transactions around the gaming pen.

Some of the best sport fishing in the

world is at hand off the coral shelves of Lanai—Ahi, Mahi-Mahi (Dolphin), giant Marlin and Sailfish, to name a few. Some mammals, such as deer and goats, are plentiful. During the months of October and November last year, over 200 deer were killed in an open season. Pheasant and Chukker Partridge are abundant, but are kept numerically under control by hunters and wild dogs. The hunting territory is extremely rugged and steep and requires stamina aplenty.

Medicine and surgery here are comparable to any community on the mainland, though some of our problems are unique. We maintain a 26-bed hospital with complete medical and surgical facilities, 5 registered nurses, a laboratory-X-ray technician, and our own drug dispensary. Our practice is principally on a fee-for-service basis through a group insurance plan supported by the Company, the local labor unions and the workers. Adequate coverage of all medical and surgical problems is assured, and seldom is an individual required to dip into his own resources for medical care. On occasion we may refer complicated diagnostic or therapeutic problems to Honolulu specialists, but generally it is a matter of pride in the plantation physicians to handle their own problems and call for help only if necessary.

The medical profession here in Hawaii represents most of the recognized schools —Harvard, Michigan, Hopkins, Columbia—and most of the physicians get back to the mainland periodically for post graduate training and to again reaffirm how lucky they are to live in Hawaii. Here on Lanai, there are two doctors handling the medical program, alternating nights on call as well as weekends. This allows a very large amount of spare time not available elsewhere. There are some 80-100 deliveries per year, 30-40 major surgical problems per year, and innumerable minor surgical and industrial problems.

In the course of a month we see 1,200-1,300 patients for all the common ailments, and since Hansen's disease is

The 26-bed General Hospital at Lanai

prevalent here, we are constantly on the lookout for early cases which are then cared for by the Territory at Hale-Mohalu Hospital on Oahu. Awareness of the possibility of Hansen's is important and is bringing the disease under control with early diagnosis, isolation and treatment. Most of the victims are returned to their families in relatively short order since the advent of Promacetin and kindred sulfone drugs.

Tuberculosis is a common disease here, and annual photo fluorograms are the rule in every community. In addition, known cases and contacts are followed in the chest clinic and periodically checked, and if necessary, hospitalized at Kula Sanatorium, a territorial hospital on the island of Maui. The T. B. we see is principally pulmonary and mostly in the older generation. Improved living facilities and education in hygiene and health seem to be having the desired effect on the problem.

The staple diet here in most of the population is fish and rice, and as a result dietary deficiencies are common. Vitamin deficiencies evidenced by peripheral neuritis, dermatitis, cheilosis and stomatitis are frequent, but fortunately most are seen early and adequate measures taken to correct the problem. The related problem of poor dental hygiene is a tremendous one and defies efforts toward radical and popu-

lation-sweeping control. Education along these lines is progressing, but slowly. The question of fluoridation of the water has been discussed and may be an early innovation. Dental caries, abscesses, pyorrhea, and associated problems are therefore common. We have one dentist who is tremendously overworked, but who is making a notable impression on the community.

Our day starts at 0730 with any elective surgery we may have, and once a year we set up a tonsil clinic for the youngsters requiring tonsillectomy. Practically all of our abdominal surgery is done under spinal anesthesia and our preference is usually pontocaine. Occasionally, it is necessary to supplement the anesthesia with pentothal, but rarely. Most of the surgery, with the exception of gastric resections, and thoracic or neuro-surgery, we do here, and as a result our experience is extremely valuable. It requires continuous study and analysis of all the common problems in diagnosis, medical and surgical treatment. Much we have carried over from medical school and internship, but we frequently introduce new methods and ideas as they are presented in the Journals. There are advantages to being situated in a Mecca of Medicine like our own Alma Mater at Harvard, but to me the challenge lies in caring for as many problems as possible without jeopardizing life and health. The prime concern lies in realizing one's capabilities and limitations and in calling for help if necessary. I fear that in most instances when immediate expert consultation is available, the problem resolves itself into "to whom will I refer the patient," and not, "how can I solve the problem myself?" Here, we are separated from the nearest "Mecca" by 80 miles and deep blue Pacific Ocean, and physical communication is possible by the one airplane a day to and from Honolulu. Telephone communication is available however, and we frequently avail ourselves of long distance and remote assistance in this manner.

Industrial accidents are infrequent because of a carefully organized and operated preventative plan. All the safety precautions feasible are utilized. One of the common problems is the "pineapple poke" caused by the needle-like leaf point of the pineapple plant penetrating gloves and fingers. This constitutes a fairly serious problem because such minor wounds commonly become infected and result in lost man hours. From an industrial standpoint, the hands create a large per cent of problems, not only on the job injuries, but eel bites while fishing. The Moray Eel is a common inhabitant of the coral shelves around the island and is therefore frequently encountered by squid fishermen. The eel is extremely unsociable and equipped with several rows of needle-like teeth which leave the appearance of having drawn the hand or foot through a meat grinder presenting a beautiful segmental picture of the anatomical structure of the

involved appendage. The problem of reconstruction can be exasperating, particularly in view of the fact that once repaired, the hand will again be exposed to repeat performance in the lair of another eel. There are other problems such as falls, contusions, occasional fractures and eye injuries, but these are common the world over.

Obstetrics and gynecology constitute a large per cent of our practice and practically all of the night work. Our experience has included most of the complications seen in the ordinary practice—breech and posterior presentations, dystocia requiring Caesarean section and a number of preeclamptics. We hold weekly prenatal clinic and maintain complete records and therefore have adequate knowledge and control over our patients. We have educated most to the use of saddle block anesthesia and have had excellent results. A valuable adjunct in labor recently has been the Duke Inhalator with the use of Trilene. We have had two neonatal deaths, both due to prematurity, since I have been here. Perhaps our luck is extremely good, but we like to attribute it to other factors. The entire obstetrical practice throughout Hawaii is more or less regulated and advised by a Board of Senior Doctors designated as the Committee on Maternal and Child Welfare. This board has done a great deal toward reducing fetal and maternal mortality.

One of the problems which must be surmounted before anything can be accomplished is the language barrier. "Pidgin" is the universal language of the Pacific area. Its origin is obscure, but its application and usefulness fully justify its development. There are many different colloquial expressions which vary from one area to another, but the concept of this mode of communication is to utilize the most direct and expressive verbalizations from Dutch, English, German, Polynesian and other dialects to convey ideas. Com-

Lanai Hospital Staff on Aloha Day, 1954. The Author is on the Far Right

monly all sentences are very colorfully enhanced by waving arms, pointing or gesticulating in descriptive effort and such sentences invariably end in, *huh?*—as if to ask understanding or verification. Pidgin here is more closely associated with English than are the more southern and western versions. A patient may not understand the query, "Does your stomach hurt?", but he immediately recognizes the doctor as a kindred soul if the same question is phrased, "You got pain in you opu maybe, huh?" It is advisable to sound out the desirable mode of conversation because it is occasionally embarrassing to address an individual in Pidgin and receive a calculated answer in the King's English with an Oxford accent. In addition, there are the pure Chinese, Japanese, Filipinos, etc. who have no working knowledge of either English or Pidgin. Here we resort to our secretary for Japanese, our druggist for Korean, ward boys for Filipino, etc. Filipino is the most difficult because occasionally it is difficult to understand the translation. All in all though, it is a lot of fun. It breaks the monotony and always some common ground of understanding can be reached, even though at times strictly pediatric methods must be utilized. It requires patience, understanding, and a knowledge of many obscure problems.

You have to come to Hawaii to appreciate it properly. Once here you almost take for granted all that is Hawaii, but when you are gone from warm climate, beautiful beaches, friendly people, their chants, ukeleles and steel guitars, you will miss every little detail of the Islands. You'll remember little incidents that almost went unnoticed; you can hear the ocean rolling in over a coral reef; the wind in the palms which sounds so much like rain that it's difficult to distinguish between the two. You'll miss the ukeleles that are distinctly Hawaiian, the wildly colored Aloha shirts that would be taboo elsewhere. But most of all you'll miss the people, a friendly, smiling, vigorous admixture of all races, a true United Nations and here and there you see distinctive racial characteristics—the liquid brown eyes of Hawaii, the beautifully delicate features of China, the figure of a hula girl, or the massive structure of a Hawaiian fisherman whom you are sure must be related to Kamehameha the Great—it's all Hawaii.

To most people Hawaii is a romantic sounding name closely akin to mythology, but to those of us here it's paradise with a a lot of common, ordinary, everyday run of the mill problems thrown in. The slow, easy, somewhat carefree way of life seems to be conducive to longevity. I suppose people here don't get tired out by living as is so true of more industrialized cities and communities. It's a pleasure to work with and for the people, to practice medicine and surgery where it's needed and appreciated.

All these things I know because I've been to the Islands and departed again several times—always of necessity. This time we're in the Islands to stay—Aloha oe nui —it's lucky when you live in Hawaii.

# *Women at Harvard Medical School*

JUNE PRYOR, '55

The pros and cons of women in medicine in general have been debated for many years now. So an up-to-date, on the spot coverage at Harvard Medical School of these controversial figures may be of interest. Naturally, women are affected in their adjustment to medical school by the attitudes and actions of their male colleagues. It is interesting in this regard to take a brief glance back over the past century; an indication of what women at Harvard may still be facing, to a limited extent, may be gleaned from earlier attitudes.

In 1847 the Faculty first asked the Corporation of the University if a woman might be admitted to the medical lectures and be permitted to take an examination for a degree. They received the rather cold reply that it was not deemed advisable to alter existing regulations of the School which implied that the students were to be exclusively of the male sex. Three years later the Corporation reversed its judgment, but the woman applying did not attend classes because of the vehement complaints of the already established male students.

A few years later the New England Hospital for Women and Children and the New England Female Medical College were organized, and in 1872 this medical college suggested that it be adopted by Harvard. Harvard, however, considered this proposal "indelicate," and the female medical college transferred its affiliations to another institution.

In 1878 Marian Hovey offered $10,000 if a woman could be admitted to Harvard Medical School on equal terms with men. Her offer was refused.

It was not until sixty-seven years after this, in 1945, that women first registered at Harvard Medical School. Incidentally, these women were considered on the same basis as the men applicants. Selection was made on the basis of college record, Medical Aptitude Test, Graduate Record Examination, general suitability for medicine, and indication of promise of success in the profession.

At the present time there is much individual variation in the feelings of fellow students and Faculty toward women in medicine. Many still reflect the conservative attitudes of the past decades. It is gratifying, however, to find that many others do not consider our presence a gross indelicacy, a regrettable break with tradition or an indication of sad psychological failure. We are sure that many of our classmates are all for us; however, somehow we get the general impression that others are not. Some were afraid that we would use our femininity to obtain special favors, prize patients, and the like. One recently voiced argument was that the presence of females inhibited the instructors to the regrettable point that dirty jokes were eliminated from the curriculum, thus abolishing what they assumed to be a most valuable mnemonic device. (To my way of thinking there is little evidence that this disaster has befallen us.)

There are certainly many minor adjustments that had to be made on our part. One of the first was learning that we were now "scholars and gentlemen" and that we, too, were to step lively to the call, "Gentlemen!" Both male and female students became more at ease when our role as colleagues rather than potential dates

became established. In a figurative sense it was learning to carry our own books, and both figuratively and literally it was learning to carry our own bone boxes. During the first two years most of the curriculum was not too dissimilar from that of undergraduate years. Of course the work was difficult for us, but it was hard work for the men, too.

The doctor-patient relationship beginning in earnest in the third year was a new one for all of us. We were all playing a new role to which we had to become accustomed. As women we have found both male and female patients generally agreeable and cooperative. I am now on the GU Service, and have seen over twenty patients without mishap, even though this would seem to be about the most delicate situation for the woman medical student in her relationship with the male patient.

Our daily routine in classes or on the wards differs in no way from that of our male classmates. However, our lives outside of school are for the most part quite different. Single girls must find living quarters, and this is definitely an added problem for new women students. Many of the girls share apartments. Although this has the disadvantage that many miss group discussions which are often valuable and stimulating, it has the distinct advantage of eliminating the mass alarm syndrome which is said to occur in Vanderbilt Hall when exams approach. A number of the girls in the various classes are married and are successfully combining housework with medical school. One third year student whose husband is at Harvard Law School is having her baby this June and has planned her fourth year program, with the help of the School, so that she will have two free months at this time.

I have a little girl five years old. She is in kindergarten this year and is certain that she will be finished with school long before I. We live in an old farm house about thirty-five minutes' drive from the Medical School, and this has the advantages of lower living expenses and surroundings more suitable for raising a young child. With soap and water, paint and paper, we have spent our spare hours transforming "the Farm" into a very livable and charming home, and painting and decorating old furniture has of necessity become one of my outstanding extracurricular activities. One of the most important problems of the woman student or physician with children is that of competent help, and a housekeeper is a virtual necessity. I am sure that it would be difficult to devote your entire thought to the problem at hand in the hospital if things were not well controlled at home. The responsibilities of managing a home under these circumstances are scarcely more time-consuming than those of single girls living in apartments or married girls who are cooking and keeping house. Time with my daughter is necessarily limited, so we both make the most of what we do have. In the evenings we have dinner together, and then there is a real children's hour with games, stories, and finally prayers.


Rapid transitions from Gray's, Best and Taylor, and Cecil and Loeb to Hans Christian Anderson and Grimm's are not difficult and have proved to be very refreshing. My days might be an hour or two longer than those of some of my classmates, but the extra hours are forgotten when I arrive home in the evening to be tackled by a blue-eyed blonde whirlwind.

In conversation it is often said that women do not justify their medical training because such a large number marry and quit the profession. This number has been variously estimated at 70 per cent, 50 per cent, and even in wilder imaginative flights at under 25 per cent. A gentleman from another university was once heard to say that in his class 50 per cent of the women dropped out; what he neglected to mention was that there were only two women in his class.

It is too soon yet to compile statistics on the number of women graduates from Harvard who are practicing in the various medical fields. However, studies have been made elsewhere, and there is no reason to believe that our statistics will not be comparable. Of 1240 women graduates from seven leading eastern medical schools, 91 per cent were found to be active in the field of medicine. 82 per cent of those married were in practice, a comparatively small drop attributable to marriage.[1] Another survey of 300 women physicians with one or more children revealed that 91 per cent of these women were active professionally. This group had a total of 637 children, an average of 2.1 per family.[2] Dr. Raquel Cohen, '49, fits well into this 91 per cent. She has had three children in the past four years, and is now a resident in child psychiatry at the Metropolitan State Hospital.

So many times we hear discussed the problem of "marriage *versus* a career." I think that this well-known phrase should be revised to "marriage *and* a career." They are not diametrically opposing forces. A kitchen stove is no more stubborn than a bunsen burner. Dr. Marjorie Kirk McKusick of the first graduating class of women writes that marriage and practice have proved to be a wonderful combination. She recently retired from

her practice of pediatrics for ten days to have her son and is now successfully combining marriage, motherhood, and practice. Dr. Ruth Weiss, '51, has found that medical training in psychiatry for a married woman with two small sons is a very busy but also extremely satisfying existence. Many of the women graduates are in the field of psychiatry; Dr. Renee Gelman, '50, is a candidate at the Institute for Psychoanalysis in Chicago; Dr. Shirley Gallup, '49, is completing her training in phychiatry at the Bowman-Gray School of Medicine; Dr. Kathleen Mero Mogul, '52, begins her residency in psychiatry next year at Boston Psychopathic Hospital. Pediatrics appears to hold second place, and Dr. Doris Bennett, '49, is busy with a young daughter, practice in pediatrics, and plans to take her pediatric specialty boards next year. Dr. Jean Dawson, '51, will also complete her training for pediatric boards this next year, and is presently working in the field of pediatric hematology.

Women graduates of Harvard are doing well in their respective professional fields. Those of us who are now in school feel that we are gradually becoming integrated and that the tendency is to accept our presence as routine. Any resistance which may still exist is general from those who studied medicine in an earlier era when fewer women were in the field of medicine. Voting privileges for women were a convention-shattering change which was only gradually accepted, and this same progression toward acceptance is occurring now with the women students at Harvard Medical School.

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[1] Downes, H. R., and Lowther, F. *Medical Woman's Journal,* 53: 39, 1946

[2] Travell, J., Reid, A. C., and Clapp, M. P. *Journal of American Medical Women's Association,* 8: 63, 1953

# *Remember These Dates*

## ALUMNI DAY AND REUNION DINNERS
## FRIDAY, MAY 28

## CLASS DAY
## SATURDAY, MAY 29

## ANNUAL DINNER
(San Francisco)
## WEDNESDAY, JUNE 23

# *Harvard Medical Society Meetings*

The program for the November meeting of the Harvard Medical Society was presented by the Medical School's Department of Biological Chemistry, Professor A. Baird Hastings presiding.

A summary of papers follows:

### Potentiometric Studies on the Diphosphopyridine Nucleotide System

F. L. Rodkey

DPN and its reduction product function in many oxidation-reduction systems but biochemists have been able to approximate the redox potential of DPN only with difficulty, and presumably with considerable error, because the substance is not electromotively active and will not impress a potential on an electrode. It is possible to work out the redox potential on the basis of equilibrium measurements but this involves certain imposing technical difficulties. Dr. Rodkey made his measurements using benzyl-viologen as mediating dye and milk xanthine oxidase as catalyst for the equilibrium between the dye and DPN systems. In this way the oxidation-reduction potential of the DPN system at 30° C. was determined potentiometrically from pH 6.5 to 10.5. Dr. Rodkey's data are in agreement with the recent equilibrium data obtained by Burton and Wilson but do not agree with the commonly accepted value calculated by Borsook.

### The Measurement of Total Glucose Phosphorylation in Normal and Diabetic Liver Slices

A. Renold, A.B. Hastings and Frances Nesbett

Since liver cells both utilize and produce glucose, it is impossible to measure accurately glucose utilization by liver slices. On the other hand, fructose utilization may be measured accurately because liver slices do not liberate fructose at a physiological pH. However, fructose is readily converted to glucose and to glycogen. By incubating liver slices with labeled fructose and labeled glucose, and by measuring glycogen synthesis from like substrates, as well as the rate at which fructose is utilized and transformed into glucose, the rate at which glucose is utilized and phosphorylated to glucose-6-phosphate may be calculated. When liver slices from normal and diabetic animals were compared, it was found that the phosphorylation of extracellular glucose to intracellular glucose-6-phosphate is 4 to 10 times less active in the diabetic than in the normal liver cell. This decreased activity was restored to normal by 48 hours of insulin administration before sacrifice. Liver slices from cortisone-treated normal animals, on the other hand, showed no decrease in their ability to phosphorylate glucose.

### Some Observations on the Action of Estradiol in Vitro

C. A. Villee and D. D. Hagerman

Earlier studies showed that estradiol-17$\beta$, at a level of $4 \times 10^{-6}$ M increases the oxygen consumption of slices of human endometrium incubated in vitro. Other experiments, with tissue slices from placentas aged 6 to 24 weeks, obtained at therapeutic interruptions of pregnancy, showed that young placenta would also respond to estradiol in vitro. Estradiol increases oxygen consumption, pyruvate utilization and the metabolism of the carbonyl carbon of pyruvate to $CO_2$. This suggested that estradiol affects the oxidative pathway of pyruvate. When the pyruvate was replaced by acetate, estradiol increased oxygen consumption and the metabolism of the

carboxyl carbon of acetate to $CO_2$. The fact that estradiol stimulates the matabolism of both pyruvate carbonyl and acetate carboxyl carbon to $CO_2$ suggests that estradiol is effective beyond the point of acetyl coenzyme A in the common oxidative pathway of pyruvate and acetate. Further studies have been made with whole homogenates or cell fractions ( mitochondria, microsome and soluble proteins) prepared from normal term placentas. The soluble protein fraction was isolated by centrifuging for an hour at 57,000 x gravity. This fraction contains all the enzymes of the glycolytic cycle and will rapidly metabolize glucose to lactic acid. Estradiol is without effect on glycolysis by this system. Placenta homogenates were incubated with glucose, pyruvate, acetate or some member of the Krebs citric acid cycle. The greatest effects of estradiol in increasing oxygen consumption were observed with glucose, acetate, pyruvate and citrate. A smaller effect was seen with alpha ketoglutarate as the substrate and none with succinate, malate or oxalacetate. The fact that no estradiol effect was observed with succinate or malate suggests that estradiol does not act on the coupled electron transmitter system but that it affects one or more of the steps early in the Krebs cycle. Although the placenta homogenates utilize oxygen at a good rate, comparable to that of placental slices, they produce little $C^{14}O_2$ from labeled glucose, acetate or carbonyl labeled pyruvate. The addition of estradiol increased the conversion of both the carboxyl and carbonyl carbons of pyruvate to $CO_2$ about 15 per cent, which is similar to the estradiol effect on oxygen consumption. Additional evidence showed that the chief intermediate that accumulates in this system is alpha ketoglutarate. The well defined estradiol effects on this system suggest that the reaction sequence citrate—cis-aconitate—isocitrate—alpha ketoglutarate is subject to hormonal influence in vitro. Centrifugation enabled the experimenters to separate nuclei and cellular debris, mitochondria and microsomes. It was shown that the supernatant containing the soluble enzymes of the cell does not utilize oxygen (for no oxidative enzymes are present) but does utilize citrate and accumulates alpha ketoglutarate, and presumably contains aconitase, isocitric dehydrogenase and oxalosuccinic decarboxylase. The effects of estradiol are marked in this system but not evident with the separated mitochondria or microsomes. That this effect can be achieved in the absence of an uptake of oxygen is further indication that the estradiol effect is localized in the Krebs cycle enzymes and not in the coupled electron-transmitter system.

**Enzymes Involved in the Metabolic Error of Alkaptonuria**

S. W. Edwards and W. E. Knox

On the basis of the hereditary abnormality known as alcaptonuria, Garrod developed, in 1908, his concept of "inborn errors of metabolism," which completely anticipated with human medical studies the field of biochemical genetics more recently developed from work on Neurospora and other lower organisms. In addition, alkaptonurics taught biochemists the probable pathway of tyrosine in man from study of the precursors giving rise to extra homogentisic acid in their urine. Recently it has been possible to confirm this proposed pathway of tyrosine metabolism and make it more precise by direct isolation and study of the successive enzymes from tissues. It has been confirmed that homogentisic acid is normally formed from tyrosine and that it is normally oxidized completely. The hereditary absence of this oxidation, which was postulated by Garrod, is therefore sufficient to account for the accumulation of homogentisic acid in these patients. The rival concept, that they formed something no one else did, is no longer tenable. Among the problems remaining to be solved in this disease are the following: Can the occurrence of osteoarthritis in this relatively simple disease, associated with the deposit of pigment in the affected

joints, teach anything about arthritis in general? What is the nature of the enzymatic error? On this second problem, the researchers have made a beginning. They have isolated and studied in normal animals the reaction lacking in the alcaptonurics. There are three enzymes acting successively. The first is a new type, an oxidizing enzyme containing ferrous iron and a thiol group, probably the prototype of a new family. It forms the previously unsuspected metabolite, maleyl-acetoacetate, the *cis* form of the recently discovered fumaryl-acetoacetate. Maleic acid itself is a potent enzyme inhibitor, but before it can be formed a cis-trans isomerase acts to convert maleyl-to the harmless fumaryl-acetoacetate. This second enzyme has glutathione as a co-enzyme. The occurrence of an isomerization of this type has been suspected also in the Vitamin A field, and its demonstration and the identification of the co-enzyme may facilitate work in that field. Fumaryl-acetoacetate is rapidly split to its component parts by a third enzyme, and the pieces enter the general metabolic reactions of the body. Absence of the last two enzymes does not result in homogentisic acid accumulation. The first enzyme must therefore be the one affected in alcaptonuria. The nature of this enzyme in normal animals is now known and can be compared with that of alcaptonurics when it becomes possible to examine the faulty enzyme of these patients. Since it is possible to recognize a gene only by the presence or absence of the character, that is, enzyme, it controls the comparison of the enzyme controlled by a normal gene with that from a mutant gene may be the most direct approach to the nature of the gene itself, it is postulated by the experimenters.

The December meeting of the Harvard Medical Society featured a program presented by members of various departments at the Children's Medical Center and at the Medical School, including the Department of Pediatrics. Dr. Charles Janeway presided.

A summary of papers follows:

**Studies on the formation and circulation of cerebrospinal fluid using stable and tracer isotopes; Edgar A. Bering, Jr., Dept. of Surgery, H.M.S., and Dept. of Neurosurgery, C.M.C.**

Tracer experiments on the cerebrospinal fluid have been carried out during the past four years with $D_2O$, $Na^{24}$, $K^{42}$ and $I^{131}$ tagged albumin. The results of these experiments suggest that the commonly accepted concepts of CSF formation need serious revision. The theory which is generally accepted that the choroid plexuses are the site of formation of the major portion of the CSF is based upon three sets of observations in addition to the clinical facts of hydrocephalus. These are the observations of Cushing on the Choroid Plexus, the experiments of Dandy and the experiments of Putnam and Schaltenbrand. Examination shows that these all have serious defects or have alternate interpretations which render them inconclusive. After intravenous injection Deuterium Oxide ($D_2O$) appears simultaneously all through the CSF. The time required for it to reach equilibrium is a function of the volume of CSF and the surface of the nervous system at the locality considered. This simultaneous appearance is true of $Na^{24}$, $K^{42}$ and tagged albumin, although there are many differences in the appearance rates of these various tracers. Tracer studies have been carried out in dogs before and after choroid plexectomy. No differences in the exchange could be found. Turnover studies in hydrocephalic dogs and in patients after tracers had reached equilibrium in the blood show that $D_2O$ and $Na^{24}$ disappear at the same rate as from the blood stream but that tagged albumin seems to be selectively stored in the CFS of hydrocephalic patients. This inability of the albumin to escape from the cerebral ventricular CSF unless the CSF circulation is

intact offers new evidence for the old concept that the CSF functions as does the lymph in other tissues in helping to remove the large molecules from the tissue fluids. This evidence would suggest that the cerebrospinal fluid is similar to the interstitial fluid of the brain and comes from the substance of the brain and spinal cord. There is considerable evidence in the literature to support this theory in addition to the evidence presented here.

**Tubular Mechanisms in the Excretion of water and electrolytes in the Nephrotic Syndrome: Jack Metcoff, J. A. James, G. Gordillo, I. Antonowicz, N. Nakasone, C. P. Rance of the Dept. of Pediatrics, H.M.S., and Dept. of Medicine, C.M.C.**

The mechanisms involved in the transport of water, sodium, potassium and hydrogen ion were studied by the technique of intravenous infusion of suitable loads in recumbent subjects. Patients selected had reversible physiologic impairment of renal functions without clinical evidence of morphologic obliteration of nephrons at the time of study. Dextran was used to study water excretion. It is a complex polysaccharide with a mean molecular weight of about 70,000. It was infused as a hyperoncotic (12%) solution in water. Effective diuresis followed 3 to 5 daily infusions in about 10 of 15 patients. Detailed studies showed that the diuresis was a water diuresis characterized, in the particular example cited, by (a) increased urine flow without change in glomerular filtration rate, (b) unchanged solute excretion and (c) a very low (8) U/P ratio for thiosulfate. Verney and Baldes and Smirk demonstrated that a rapid fall in osmolarity of the extracellular fluid of 1.5-2% initiates diuresis through inhibition of secretion of antidiuretic substances mediated by osmoreceptors. In the dextran studies, osmolarity of the E.C.F. was acutely decreased as much as 4-5%. The authors indicated that it was not possible to determine whether decreased elaboration or dilution of antidiuretic substances, or both, resulted from plasma volume expansion, or whether the extremely dilute urine resulted from failure of water reabsorption or from secretion of water by the distal tubule. It was apparent from the data that dextran-induced diuresis was not due to inability of the renal tubules to respond to antidiuretic substances because the intravenous injection of pitressin inhibited the diuresis. The failure of a profound increment in plasma volume (+36%) to alter the glomerular filtration rate, although it produced a rise in renal plasma flow (hence a fall in the filtration fraction), suggested that the increased hydrostatic filtration pressure was counterbalanced by the increased colloid osmotic pressure from retained dextran. The authors also postulated that the observed diuresis may have resulted from stimulation of some intrarenal regulator of water reabsorption by increased post-glomerular flow of blood having an increased colloid osmotic pressure.

The intravenous infusion of non-reabsorbable anion loads was used to examine mechanisms of cation excretion. Because the excretion of sodium may be limited during edema, similar observations made on patients during the profuse sodium diuresis of edema fluid and again on the same patients when non-edematous allowed the authors to characterize some features of renal electrolyte transport in children with the nephrotic syndrome. The detailed observations showed that (a) there was an increased tendency to lose potassium, often caused by renal tubular secretion of potassium during the loads; (b) the excessive excretion of potassium was independent of the level of reabsorption of sodium; (c) under stress of an obligatory anion load superimposed upon infusion of an inhibitor of carbonic anhydrase (6063), the nephrotic patients secreted potassium while sodium reabsorption decreased and the urine became acid (increased $H^+$ excretion). The authors postulated that some aberrant or alternate pathways for renal potassium transport may exist during nephrotic edema other

than one in which $H^+$ and $Na^+$ are competitors.

**Responses in Lymph Nodes of Normal and Agammaglobulinemic Children to Antigenic Stimulation, John Craig and David Gitlin, Dept. of Pathology, H.M.S. and C.M.C., Dept. of Pediatrics, H.M.S., and Medicine, C.M.C.**

Some 16 cases of congenital absence of gamma globulin in the serum are now known. This syndrome is characterized by repeated severe infections coming early in life, by failure of antibody response to injected antigen, by the absence of isohemagglutinins and by normal disappearance rates of injected gamma globulin. There is some evidence that the syndrome is hereditary.

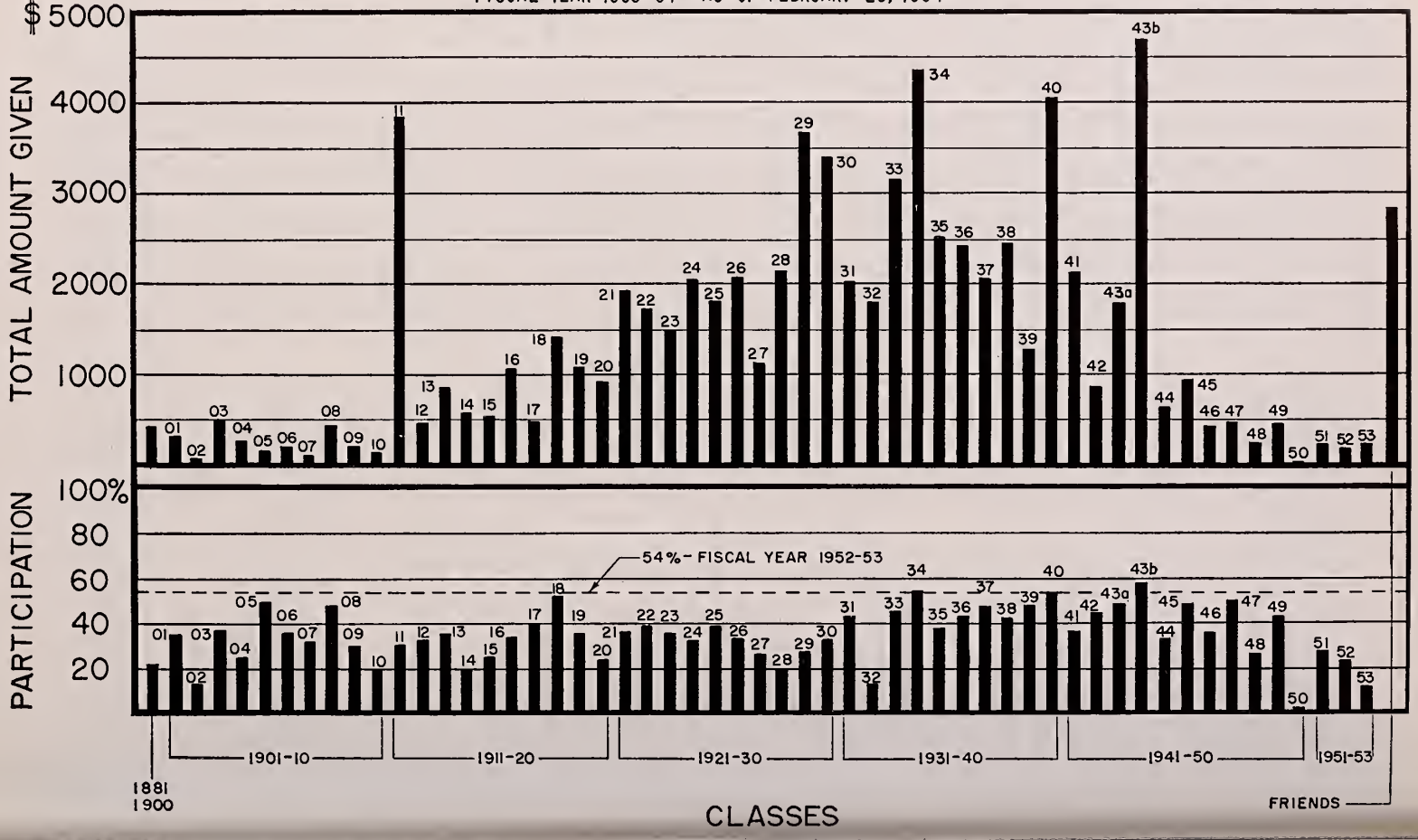
Lymph nodes removed at herniorrhaphy from normal children four days after injection of antigen show the development of a broad cortex, well developed germinal centers and secondary centers. The cortex and the medullary cords show the presence of numbers of plasma and pre-plasma cells. Sections of these nodes examined by the Coons fluorescent labelled antibody technique for the presence of gamma globulin show it to be present in easily demonstrable amounts. Lymph nodes from similarly treated children with congenital agammaglobulinemia show a narrow cortex, no well defined germinal centers and a virtual absence of plasma and pre-plasma cells. These nodes when examined by the Coons technique show the presence of antigenic material but an absence of demonstrable gamma globulin and specific antibody.

**Studies on the Etiology of Varicella and of Herpes Zoster, Thomas H. Weller, Dept. of Tropical Public Health, Harvard School of Public Health, and Research Division of Infectious Diseases of C.M.C.**

Serial propagation of the etiological agent of varicella has heretofore not been accomplished. The focal lesions described by Rivers following inoculation of varicella vesicle fluid into the monkey testicle provide the sole indication that the responsible agent has been transmitted to an experimental animal. In 1948, we explored the use of suspended cell cultures of various human embryonic tissues for the isolation of this agent. Following inoculation of such cultures with varicella vesicle fluid, eosinophilic intranuclear inclusions could be demonstrated in fragments of tissue removed from the cultures. Efforts to maintain the agent on serial passage were unsuccessful, however. More recently roller tube cultures of human tissues have been applied to the same objective. In cultures of this type focal areas of degeneration develop following inoculation with vesicle fluid materials. The focal lesions, which slowly increase in size, are characterized by the appearance of round, swollen cells, which on staining manifest eosinophilic intranuclear inclusions. By employing tissue suspensions as the inoculum seven strains of the agent responsible for these morphologic changes have been subcultured, and two strains have been propagated serially for twelve passages in roller tube cultures. Suggestive evidence indicating that the agent thus propagated is, in fact, the etiological agent of varicella, has been obtained through the use of tissue culture materials as antigen in complement fixation tests. Furthermore, preliminary studies done in collaboration with Dr. Albert Coons and employing his fluorescent antibody technique, indicate that the focal lesions in the cultures do not fluoresce in the presence of acute phase serums from patients with varicella, but do fluoresce when convalescent phase sera are present. From the vesicular lesions of patients with herpes zoster, agents also have been isolated that have been propagated serially in roller cultures. These produce changes similar to those found in cultures inoculated with varicella materials. It now appears that methods are available whereby the possible co-identity of the viruses of varicella and of herpes zoster may be proved or disproved.

# HARVARD MEDICAL ALUMNI FUND
# REPORT OF ANNUAL GIVING

FISCAL YEAR 1953-54 AS OF FEBRUARY 28, 1954



# *A Message from the Director of Alumni Relations*

On the opposite page is a graph showing the progress by the Alumni in annual giving to the School. We are now in the third year of this effort and there remain about three months before our fiscal year ends on July 1, 1954.

The lower part of the graph shows the percentage of participation by classes, and it is scored against the over-all average participation of last year, which was 54 per cent. In an effort such as this, the per cent of participation is as important as the total amount given. If it can be shown that the doctors themselves are whole-heartedly behind this effort to provide good medical education, we are then in a much better position to influence help from industry. The total amount given is $78,253.98 as compared with $70,278.55 at this time last year. The average gift is $40.77 as compared to $37.28. The size of any gift is a very personal decision. Any gift, however small, is most welcome. The larger gifts in general come from those in their years of peak earning. Two of the four highest class totals include very substantial single gifts. One of the most encouraging features is the significantly rising amounts that come from "Friends." This is a field that can be developed to a very significant extent.

The money the Alumni raise is not only very significant in amount, but is of tremendous help to the School because it is for unrestricted use. It represents the income on a very large amount of capital funds. One of the greatest values is in providing more adequate pay for the teaching staff.

Over the past ten years, the salaries of the teaching staff have been increased on the average by about 25 per cent. With the decreasing value of the dollar, however, this has left the members of the teaching staff *worse off* in purchasing power than they were ten years ago. On the average, the wages of non-teaching employees have more than doubled in this same period. So we hope you will consider these facts, and if you have not contributed, please try to do so.

THOMAS H. LANMAN, M.D.

# *Dr. Stanley Cobb Retires*

The portrait on the cover is of one of Harvard's most distinguished Medical Alumni. Stanley Cobb retires this June as Bullard Professor of Neuropathology and head of the department of psychiatry at the Massachusetts General Hospital.

He was born in Brookline on December 10, 1887. He received his A.B. from Harvard College in 1910, and his M.D. from Harvard Medical School with the Class of 1914, 40 years ago. Upon graduation, he served as surgical house officer at the Peter Bent Brigham from 1914 to 1915. This was followed by a year's work in the laboratories of Johns Hopkins, where he was successively an assistant in physiology and later in psychiatry, and was much interested in the physiology of the nervous system. During 1917 and 1918 he was an associate in psychiatry at the Johns Hopkins Medical School. In 1919 he returned to Boston, his first position being that of Dalton Scholar and assistant neurologist at the Massachusetts General Hospital, as well as instructor in neurology and physiology at Harvard Medical School. From then on he continued here in Boston and rapidly rose to the rank of assistant professor in 1919, associate professor in 1923, and since 1926 has been Bullard Professor of Neuropathology. He was a First Lieutenant in the Medical Corps in the first World War. He traveled in Europe in 1923 and 1925 as a Rockefeller Fellow and in addition to his work at the Massachusetts General Hospital and the School, he was neurologist at the Boston City Hospital from 1925 to 1934. He has been chief psychiatrist at the Massachusetts General Hospital since 1934.

Dr. Cobb's memberships in learned societies include the American Neurological Association, of which he was president in 1948, the Association of American Physiologists, the Association for Research in Nervous and Mental Diseases, the American Society for Clinical Investigation, and the American Psychiatric Association.

The Bulletin takes pleasure in acknowledging Dr. Cobb's forty years of outstanding service to the profession and to the Harvard Medical School.

# *A Change in Personnel*

Kay talks with J. Englebert Dunphy, '33, David Kliewer, '51, and Philip Wilson, '12, on Alumni Day, 1951

A familiar face is missing from the Alumni Office this year. Mrs. Katherine B. Wilson—"Kay" to so many Alumni—has left after 18 years serving the Harvard Medical Alumni Association. Kay's new address is Greensboro Road, Hanover, N. H. As a symbol of appreciation of her devoted service on behalf of the Association, the Alumni Council presented her with a handsome silver cigarette box appropriately inscribed:

Katherine Bullard Wilson
Executive Secretary
1935 1953
with appreciation and affection
from
The Harvard Medical Alumni Council

The many Alumni who knew Kay Wilson during her term of service at the School join us in wishing her all success.

# *Regional Activities*

MILWAUKEE

On February 16, 1954, Dr. Mark Altschule, '32, in Milwaukee to address the Milwaukee Academy of Medicine, spoke to the Alumni in the Milwaukee area. Dr. Arthur A. Holbrook, '32, made the arrangements.

BIRMINGHAM

Dr. J. Englebert Dunphy, '33, met for luncheon at The Club in Birmingham with the Alumni in that area on March 9, 1954. Dr. Paul Salter, '45, and Dr. B. Hughes Kennedy, '21, arranged the gathering. Dr. Dunphy was in Birmingham to speak at the Southeastern Surgical Congress on "Treatment of Acute Massive Gastro-Intestinal Hemorrhage."

LOS ANGELES

The Alumni of Southern California met with Dr. Francis D. Moore, '39, for dinner at the University Club of Los Angeles on March 3, 1954. Dr. Moore was in the city for a series of lectures at the Surgical Forum of Los Angeles. The meeting was planned by Dr. Lowell F. Bushnell, '33.

NEW YORK

The Harvard Medical Society of New York held their spring dinner meeting on March 11, 1954 at the Harvard Club. There were nearly a hundred members and guests present. The speaker of the evening was Mr. Jerome S. Meyer, author and amateur graphologist, who spoke on hand-writing analysis. President George Wheatley, '33, presided. The officers for the year 1954 were elected, and are: President—Dr. John N. Robinson, '31; Vice-president—Dr. Howard A. Patterson, '25; Sec'y-Treas.—Dr. Kenneth W. Thompson, '29. The new officers again remind the Harvard Medical Alumni living in the New York area that they are invited to meet with this group for the pleasure of renewing associations with the School.

**FUTURE MEETINGS**

ROCHESTER, NEW YORK

On May 14th, 15th, and 16th, the Associated Harvard Clubs will be the guests of the Harvard Club of Rochester, New York. Saturday afternoon is devoted to a series of group meetings of a special interest to the various graduate schools. The Harvard Medical School meeting, thanks to the cooperation of Dr. Donald Anderson, Dean of the University of Rochester School of Medicine and Dentistry, will be held at the Rochester Medical School. Dr. Thomas H. Lanman, '16, Director of Alumni Relations, has been asked to take part in a panel on medical education. That evening the Annual Associated Harvard Clubs Banquet will be held at the Hotel Sheraton. All Alumni are cordially invited. This will give many Harvard men their first chance to hear from the new President of the University, Mr. Pusey.

# *Meeting of the Alumni Council*

On Saturday, February 27, the Harvard Medical School Alumni Council convened at 25 Shattuck Street for the second stated meeting of the year. In addition to assembling to conduct necessary business for the Association, the Council expressed their view that they would be interested in being kept abreast of new developments going on at the School.

Assembling in the Faculty Room, the Council was greeted by Dr. Arthur Hertig, Shattuck Professor of Pathological Anatomy, who then spent a short time touching upon the highlights of his department's reorganization and the new approach to teaching pathology. From here the Council was taken to Building D where Dr. Hertig and his colleagues took the group on an extensive tour of the department. They had a chance to see how valuable space and facilities had been reclaimed by carefully planned partitioning and re-arrangements, thus getting maximum efficiency from the old high-studded laboratories that the Council had known. Following this tour, the Council, with the pathology staff, adjourned for luncheon at Vanderbilt Hall.

# *John Howard Mueller*

**1891-1954**

Howard Mueller was the third to occupy the Chair of Bacteriology and Immunology. As successor of Frederick Ernst and Hans Zinsser he maintained and enhanced the respect with which this comparatively young department early came to be held by microbiologists throughout the world. This he did in the main—or so it seems to me, his long-time friend and fellow worker—through his complete dedication to the search for truth by means of the experimental method. His ardent belief in this basic code of the scientist influenced also profoundly his attitudes and ideas in respect to the non-scientific world. It gives the key not only to much that was valuable and admirable in his character but also to traits, such as his impatience with the unclear of thought or his reluctance to compromise, that were not always regarded as virtues by those who failed to understand the principle that guided him

Howard Mueller belonged among the scientific "elite" as Kirtley Mather has recently defined them—that is among those who actively seek insight and meaning, whose minds are constantly on the alert to the possibility of new generalizations and new relationships as distinguished from those who merely know how to do that which they have been trained to do. A synopsis of his life's work reveals his right to be numbered among this company. After graduation in 1912 from Illinois Wesleyan University with honors in biology, he taught as instructor in physiological chemistry at the University of Illinois for two years, when he took the degree of M.S. While in Louisville he likewise found time to attend courses in pathology and bacteriology. During the summer of 1914 in order to gain further knowledge of pathology which evidently had keenly aroused the interest of the young chemist, he attended a course in that subject at the College of Physicians and Surgeons of Columbia University. His brilliant performance led his instructors to encourage him to continue as a graduate student. In 1916 he was awarded the Ph.D. degree in pathology having elected as minors biochemistry and bacteriology. These biographical data reveal one who during his predominantly educational years was seeking to strengthen his insight into the chemistry of disease which, broadly interpreted, remained the major preoccupation of his career, by acquiring a thorough knowledge of the development and appearance of pathological changes.

Later as well, Howard Mueller, ever alert to the possibility of new relationships and unlike many non-physicians who devote themselves to the study of one aspect of medicine, continued to seize every opportunity to maintain contact with the practical problems of diagnosis and control of disease as they present themselves at the autopsy table, in the clinical laboratory, and in the field. Thus after receiving his doctorate he served for a year as Assistant and Resident Pathologist at the Presbyterian Hospital in New York and taught pathology at the College of Physicians and Surgeons. During the war of 1917-1918 he enlisted as a private and later became a lieutenant in the Sanitary Corps attached to the Presbyterian Base Hospital Unit. He served in France for two years as one of the laboratory staff and for a time as Director of the Laboratory. Again, many years afterwards, he responded with characteristic vigor and effectiveness to a call for assistance from the Public Health authorities in Halifax where, in 1941, a serious epidemic of diphtheria had been in progress for several months. At the head of a team of younger men and women which he quickly assembled he contributed both by word and deed toward the eventual control of this outbreak. The experience with diphtheria gained in Halifax was valuable when, immediate-

ly after the Second World War, he was called upon to make recommendations for the management of this disease which was then occurring with disturbing frequency among our troops stationed in Germany.

Such activities illustrate the breadth of his interests and his sense of the essential unity of the sciences. But it was always to the chemistry of living things that he returned and to which he gave the best of his mind and indeed of his heart. With the foresight of the pioneer he early decided that bacteria afforded eminently suitable material for biochemical investigation because of their unicellular nature, the rapidity of their growth and the ease with which the conditions of this multiplication can be controlled. His practical instinct led him to select certain pathogenic organisms for study since he perceived that increase in knowledge of their metabolism would in all probability not only parallel in fundamental ways that of higher forms but also might reveal new or improved approaches to the prevention and therapy of infectious disease. There can be little doubt that these considerations were paramount, when upon his return from France in 1919, he decided to accept Hans Zinsser's invitation to become, as assistant professor, a member of the department of bacteriology at Columbia. Then were initiated the long series of investigations on bacterial metabolism that were to continue until his death, and which in accordance with his prediction have yielded results of the greatest significance.

Beginning with an exploration of the nutritional requirements of the hemolytic streptococcus, he soon observed that a sulfur-containing component of a protein hydrolysate appeared to be essential for the growth of this organism. Since this component did not contain cystine or cysteine—the only sulfur-containing amino acid then known—he proceeded to isolate and identify the active principle. This was no easy task. Before it was completed three years were spent in acquiring a mastery of unfamiliar techniques and in applying them to the analysis of the complex material involved. Yet it was well worth the effort, because the unknown factor proved to be the amino acid methionine which is essential for the synthesis of choline and creatine in the body. This compound has proved to be of such importance in the economy of living things that many competent judges consider its isolation and identification as the most significant of Howard Mueller's contributions to science and medicine.

The rest of these contributions were made during the thirty-one years that he studied and taught as Associate Professor and Head of the Department of Bacteriology, at the Harvard Medical School. Most of them were outstanding, and their influence is still felt and will continue to be felt in the progress of the disciplines to which they pertain. But here they can only be briefly mentioned. In collaboration with Zinsser he prepared from extracts of pneumococci and tubercle bacilli the substances at first termed "residue antigens" which were later shown to be complex polysaccharides. Similar observations were reported simultaneously and independently by Avery and his coworkers at the Rockefeller Institute. Formerly it was held that only proteins could act as antigens. Since these new materials also were found to behave as antigens this view had to be modified. Intensive study by others of the polysaccharide antigens has led to advances in immunological knowledge.

At about this time he was also engaged in an attempt to confirm the experiments of Gye who had presented evidence that two factors were involved in the production of tumors by the Rous sarcoma virus —one, the virus itself, the other, a more stable non-living principle. Several years of hard work were spent on this problem which ended in the publication of a joint paper containing two opposing sets of conclusions—one by Gye, the other by Howard Mueller. The latter found himself entirely unable to interpret the results in favor of Gye's hypothesis. Subsequent events showed him to be quite correct. This unusual manner of presenting a sci-

entific paper admirably reveals his uncompromising scientific integrity and at the same time his respect for the considered opinion of others and his sense of fair play.

The interlude of the Rous virus at an end, he undertook the analysis of the growth factors for the diphtheria bacillus which eventually terminated in complete success. A medium of known composition was made available which has been of much value in the production of toxin for purposes of immunization since it provided a means of preparing toxoid free of large protein derivatives and led to the revelation by others of the controlling role of iron in the formation of the toxin. Even more important, perhaps, were the discoveries that pimelic acid, nicotinic acid and beta-alanine were essential growth factors for this organism. These observations preceded the demonstration that nicotinic acid exerted a therapeutic effect in pellagra and that beta-alanine is a constituent of pantothenic acid.

Comparable investigations with the tetanus bacillus carried on during the Second World War and afterwards until his death have defined more clearly if not completely the factors involved in the growth and toxin formation of this organism and so have materially assisted in improving the quality and facilitating the production of the invaluable tetanus toxoid.

I have dwelt at length on his scientific activity because it was productive of distinguished achievement and because it formed the core of his life. Indeed, it is impossible to think of him for very long outside his laboratory. But this was by no means all. To his friends, pupils and associates he was a man quite as interesting and compelling as his work. His mental energy was equalled by his extraordinary physical vigor. This fortunate combination enabled him to work long hours in the laboratory while it provided him with the force to accomplish many other tasks and to enjoy to the fullest his times of relaxation. His teaching whether in the lecture hall or more informally in the students' laboratory was distinguished by clarity and terseness frequently enlivened by the judicious interjection of a witty remark. He was keenly aware of his responsibilities for the instruction of medical students and constantly strove to maintain an effective balance between the attention devoted to those aspects of bacteriology and immunology he knew would be of immediate practical value to the future practitioner and those of a more general character. With his graduate students either singly or in groups he spent much time in discussion of their problems, helping, criticizing and sometimes exhorting. At intervals he escaped from this intensive activity of the laboratory by flights to his camp in the woods near Halifax. There with a dry fly he pursued the trout with the same intelligent enthusiasm and skill that he brought to the hunt for an elusive growth factor. Shorter respites were gained on his place in West Roxbury where he gradually converted with tractor and shovel three stony acres into green lawns shaded with apple trees. Like many of his kind he was refreshed by music and in early boyhood studied the violin which he continued to play throughout his lifetime. It is in entire accord with his nature that Bach gave him the greatest delight.

Death has a way of suppressing among the shadows the trivia and defects of a good man's character while it throws his virtues into high relief. And so it is with him. We see him now even more clearly and the sight in these confused days is reassuring. We see first his integrity that was quite unwilling on any level to yield to the half-truth or the devious way. Closely related was his scorn of the pretentious, the glib or the slovenly wherever found in person or in thing. Younger colleagues and graduate students for a time might feel this quality burdensome as they were obliged to rewrite their papers or theses over and over again. Yet in the end they gladly acknowledged its beneficent effect.

He was humble in the way of all true

scientists. Half humorously he would often refer to himself as "a high school chemist," but underneath he knew that in the presence of the infinite complexity of living things a high school chemist is about all he or anyone else, at least for a long time, may claim to be.

His manner of living was simple as suits the investigator and teacher. His industry was the wonder and envy of his fellow workers. It was his custom to arise very early—often around four o'clock—and go to the laboratory where he continued to work and teach until the evening. And he was deeply charitable. All of us who knew him have heard, usually long after the event and in a round-about way, of his helpfulness in times of need or distress to many of those who worked with him. His kindliness, along with understanding sympathy whenever appropriate, took a tangible form. These acts he painstakingly tried to conceal. It was only here that I ever knew him to be consciously deceptive. We may rejoice at this single lapse from the guiding rule of his life.

JOHN F. ENDERS, M.D.,
*Associate Professor of Bacteriology and Immunology*

# *Necrology*

**1894**

ALONZO CARTLAND FALES died at Wolfville, Kings County, Nova Scotia, Canada, November 24, 1953.

FRANK OSCAR HIGBEE ('90-'92) died at Gary, Indiana, June, 1953.

GEORGE BANCROFT SARGENT died at Lawrence, Massachusetts, February 11, 1954.

**1895**

WILLIAM HENRY ROBEY died at Boston, Massachusetts, February 23, 1954.

**1899**

FRED ROBERT JOUETT died at Cambridge, Massachusetts, January 30, 1954.

**1900**

CHARLES FENNER ATWOOD died at Lexington, Massachusetts, February 6, 1954.

**1901**

ROBERT EUSTIS HOYT died at Bethesda, Maryland, December 19, 1953.

SAMUEL GRAHAM UNDERHILL died at Santa Barbara, California, December 31, 1953.

**1902**

EDWARD STOCKBRIDGE GUSHEE died at Meriden, Connecticut, February 22, 1954.

**1903**

JOSEPH STANTON died at Newton, Massachusetts, January 2, 1954.

WINSOR MARRETT TYLER died at Brookline, Massachusetts, January 9, 1954.

**1904**

CHARLES PERLEY GRAY died at New York City, December 8, 1953.

**1905**

WILLIAM PARSONS BOARDMAN died at Pembroke, Massachusetts, March 1, 1954.

**1906**

PHILIP HASKELL SYLVESTER died at Damariscotta, Maine, March 12, 1954.

CHARLES SAMPSON TURNER died at Cranston, Rhode Island, November 9, 1953.

**1908**

GUY C. LANE died at sea, March 12, 1954.

**1915**

GEORGE FRANCIS DWINELL died at Manchester, New Hampshire, January 4, 1954.

**1918**

ALFRED SMITH O'CONNOR ('14-'16) died at Worcester, Massachusetts, January 15, 1954.

FRED SANBORN THORNE died at Newton, Massachusetts, December 6, 1953.

**1922**

WILLIAM FRANTZ HARPER died at Selma, Alabama, January 1, 1954.

**1925**

SUTHERLAND ERIC SIMPSON died at Watertown, New York, January 8, 1954.

**1944**

ALVIN THEODORE HELD died at Decatur, Illinois, December 8, 1953.

**1952**

EUGENE A. BERNSTEIN died at Boston, Massachusetts, January 7, 1954.